REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1, 2, 4-7 and 9-13 and 15-20 are pending after entry of the amendments set forth herein.

Claims 1-20 were examined. Claims 1-20 were rejected. No claims were allowed.

Claims 1, 7 and 9-11, 13 and 15-17 and 20 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to the claims is found in the claims as originally filed, and throughout the specification. Claim 1 has been amended to recite the subject matter of claim 3 and claim 8. As such, support for the amendment to claim 1 may be found in claims 3 and 8, as originally filed. Support for further amendments to claim 1 may be found in Tables 6, 7 and 8 on pages 36, 38 and 40, respectively, where support for a comparison of reporter gene construct expression between experimental and controls cells may be found. Support for the word "significant" in claim 1 may be found in paragraph 73 on page 30. Claims 11, 17 and 20 are amended to recite "yeast". Support for "yeast" may be found in claims 3, 8 and 14 as originally filed. Because claims 3, 8 and 14 were cancelled, the dependency of claim 9, 10, 15 and 16 was amended accordingly. Claims 17 was amended to correct the spelling of the word "microorganism". Accordingly, no new matter is added by these amendments.

Please replace claims 1, 7 and 9-11, 13 and 15-17 and 20 with the clean version provided above.

Claims 2, 3, 5, 6, 8, 14 and 18 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Objection to the Specification

The Office Action states that specification was objected to, assertedly because it contains embedded hyperlinks.

This objection has been addressed by amendments to paragraphs [0015], [0016], [0064], [0090], as shown above. Applicants respectfully request that this objection be withdrawn.

Rejection of claims under 35 U.S.C. § 112, first paragraph-enablement

The Office Action states that claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. In making this rejection, the Office stated that the specification is enabled for methods that involve *yeast*. Applicants respectfully traverse the rejection.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

Applicants respectfully submit that many components, e.g., those for transcription, translation, protein folding and modification, stress responses, heat shock, signal transduction, etc, are conserved among eukaryotic cells. Because these components are conserved, one of skill in the art would recognize that eukaryotic cells other than yeast can be used in the claimed methods. In other words, one of skill in the art would reasonably expect to be able to practice the methods as claimed using a variety of eukaryotic cells. The subject methods require nothing more than detecting expression of a stress-response gene in a host cell containing a heterozygous deletion. Since methods of making heterozygous deletion mutants are known in most model eukaryotes, and a variety of stress related genes are known in most model eukaryotes, one of skill in the art would merely have to detect expression of the stress response gene in response to candidate compound in such cells to practice the subject methods. Furthermore, the inventors have described several suitable stress response genes in Table 7, on page 38 and 39 of the specification. Almost all of these genes all encode chaperones. Since chaperones are also found in other eukaryotes, one of skill in the art would be able to identify suitable stress response genes in other eukaryotes, *without* undue experimentation. As such, one of skill in the art would practice the claimed methods in other eukaryotes without undue experimentation.

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

Nevertheless, and solely in the interest of expediting prosecution, claims 1, 11, 17 and 20 have been amended to recite "yeast".

Applicants respectfully submit that this rejection has been adequately addressed by these amendments to claims, especially in light of the Office's statement that the specification is enabled for methods that involve yeast. Withdrawal of the rejection is respectfully requested.

Rejection of claims under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 3, 5-7 and 11-16 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitations of claim 3 have been incorporated into claim 1. Claim 1, as amended, recites "host cell contains a heterozygous deletion..." and not "host cell is contains a heterozygous deletion...". Further, Claim 1, as amended, recites the phrase "no significant increase in expression of the stress response gene as compared to expression of the stress response gene in a control host cell" and does not recite "...relatively low...increase in expression of the stress response gene...". What is meant by "no significant increase" is described in detail in paragraph 73 of page 30 of the specification. The claim, as amended, clearly defines which gene expression levels are compared to make a determination of no significant increase. Applicants respectfully submit that the meaning of this phrase is clear.

Claims 3, 5 and 6 are cancelled, and, as such this rejection of claims 3, 5 and 6 is moot.

In claims 7 and 13, the phrase "each strain" has been amended to recite "each host cell". Applicants respectfully submit "each host cell" finds antecedent support in each claim.

In claim 11, the word "low" has been amended to "lower". In this claim, the word "lower" appears in the phrase "lower or undetectable level of expression of the stress response gene in the host cell relative to a level of expression in a wildtype host cell exposed to the bioactive compound". The word "lower" is a relative term, and the phrase in which the word is found explains which levels of expression should be compared relative to each other in order to make a determination of "lower". As such, Applicants respectfully submit that the meaning of the phrase is clear.

Applicants respectfully submit that the rejection of claims 3, 5-7 and 11-16 has been adequately addressed in view of the remarks set forth above. Accordingly, the rejection may be withdrawn.

Claim rejections under 35 U.S.C. § 102

Claims 1, 2, 4, 5 and 17 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bianchi et al (Appl. Env. Microbio. 65:5023-5027, 1999). Claims 1, 2, 4, 5, 8, 9 and 17 are rejected under 35 U.S.C. § 102(b) as being anticipated by Adams (J. Bact. 173:7429-7435, 1991).

Claims 2 and 5 are cancelled, and, as such this rejection of claims 2 and 5 is moot.

Claim 1 has been amended to incorporate the limitations of claim 3. Since Bianchi or Adams are deficient in that they do not disclose all the limitations of claim 3, Bianchi and Adams are deficient in that they do not disclose all the limitations of claim 1, as amended. As such, Applicants respectfully submit that Bianchi and Adams cannot anticipate the subject matter of claim 1.

Claim 4 is dependent on Claim 1, and, as such, also contains limitations that are not met by the disclosures of Bianchi and Adams. Applicants respectfully submit that Bianchi and Adams cannot anticipate the subject matter of claim 4.

Claim 17 has been amended to incorporate the limitations of claim 18. Since Bianchi or Adams are deficient in that they do not disclose all the limitations of claim 18, Bianchi and Adams are deficient in that they do not disclose all the limitations of claim 17, as amended. As such, Applicants respectfully submit that Bianchi and Adams cannot anticipate the subject matter of claim 17.

Applicants respectfully submit that the rejection of claims 1, 2, 4, 5 and 17 has been adequately addressed in view of the remarks set forth above. Accordingly, the rejection may be withdrawn.

Claim rejections under 35 U.S.C. § 103

Claims 18-20 are rejected under 35 U.S.C. § 103 as being obvious in view of Bianchi et al., assertedly because one of skill in the art would be motivated to have used the method of Bianchi et al to detect sensitivity of bacteria from a biological sample to a drug.

It is well known that in order for a proper *prima facie* case to be established, a reference or a combination of references must teach or suggest all of the claim limitations, there must be a motivation to combine the references, and there must be some expectation of success in combining the references.

Claims 18-20, as amended, are directed to methods that involve yeast cells.

Bianchi discloses methods that solely involve *E. coli* cells and does not disclose, teach, or suggest methods that involve yeast cells. Since Bianchi fails to disclose, teach or suggest methods involving yeast cells, Bianchi fails to teach a claim limitation of claims 18-20 and, as such, a *prima facie* case of obviousness cannot be established. Accordingly, this rejection may be withdrawn.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-153.

Respectfully submitted,
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Date: January 17, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Paragraph [0015] on page 6 is amended as follows:

--Functional Classification of the *S. cerevisiae* Genome by Gene Deletion and Parallel Analysis in Winzeler, E. *et al.* (1999) *Science* 285:901-906, see also **the Stanford University yeast deletion project worldwide website at stanford.edu/group/yeast_deletion_project/deletions3.html**. ~~**http://sequence-www.stanford.edu/group/yeast_deletion_project/deletions3.html**~~.--

Paragraph [0016] on page 6 is amended as follows:

--The complete sequence of the genome of *S. cerevisiae* is available from **the Stanford University Saccharomyces genome worldwide website at stanford.edu/Saccharomyces,** ~~**http://genome-www.stanford.edu/Saccharomyces/,**~~ and is discussed in Goffeau, A *et al.* (1996) *Science* 274:563-567.--

Paragraph [0064] on page 25 is amended as follows:

--The strains used in the screening method can vary from a single strain altered in expression of a single target gene to a collection of strains representing a selected set of target gene deletions (e.g., a set of genes involved in a selected signaling pathway or members of a selected protein family (e.g., kinases)). In one embodiment, the method of the invention employs a complete genomic set of genetically tailored yeast strains potentially sensitized or resistant to every possible drug target coded by the yeast genome, with each strain carrying a deletion of a single genetic locus. A fifteen-lab international consortium is currently carrying out production of a collection of tagged heterozygous deletion strains. This collection of bar-coded deletions is available at **the Stanford University yeast deletion project worldwide website at stanford.edu/group/yeast_deletion_project/deletions3.html** ~~**http://sequence-www.stanford.edu/group/yeast_deletion_project/deletions3.html**~~.--

Paragraph [0090] on page 37 is amended as follows:

--The results are summarized in Table 6. The fold induction of the indicated stress response gene is relative to expression levels in the absence of exposure to the indicated stimuli. Conditions other than tunicamycin were obtained from **the world wide website of Incyte at proteome.com/databases/YPD** ~~**http://www.proteome.com/databases/YPD**~~, or from other published data (FK506 data from Marton *et al.* (1998) *Nature Medicine* 4:1293, diauxic shift data from DeRisi, J. *et al.* (1997) *Science* 278:680-686, heat shock data from Roth, F.P. *et al.* (1998) *Nature Biotechnol.* 16:939-945 and MMS data from Jelinsky, S.A. and Sampson, L.D. (1999) *Proc. Natl. Acad. Sci. USA* 96:1486-1491). Information on various genes and open reading frames were obtained from the Yeast Proteome Database (YPD) (Costanzo, *et al.* (2000) The Yeast Proteome Database (YPD) and *Caenorhabditis elegans* Proteome Database (WormPD): comprehensive resources for the organization and comparison of model organism protein information. Nucleic Acids Research 28(1): 73-76. --

IN THE CLAIMS

Claims 1, 7 and 9-11, 13 and 15-17 and 20 are amended as shown below.

Claims 2, 3, 5, 6, 8, 14 and 18 are cancelled without prejudice to renewal.

1. **(Amended)** A method for identifying a bioactive compound, the method comprising the steps of:

contacting a **yeast** host cell **containing a heterozygous deletion in a target sequence** with a candidate bioactive compound; and

detecting expression of a stress response gene by the host cell in response to said contacting;

wherein detection of no significant increase in expression of the stress response gene as compared to expression of the stress response gene in a control host cell indicates that the candidate bioactive compound has activity as a drug and that the host cell having the heterozygous deletion is sensitive to the drug activity of the compound.

~~**wherein expression of the stress response gene indicates that the bioactive compound has activity as a drug.**~~

7. **(Amended)** The method of claim ~~**6**~~ **1**, wherein at least two or more host cells, each having a heterozygous deletion in a different target sequence, are contacted with a candidate drug in a single culture, and wherein expression of the reporter gene construct in each ~~**strain**~~ **host cell** provides for a unique detectable signal for detection of reporter gene expression.

9. **(Amended)** The method of claim **81**, wherein the stress response gene is selected from the group consisting of *HSP26*, *HSP12*, *HSP42*, *HSP78*, and *HSP82*.

10. **(Amended)** The method of claim **81**, wherein the stress response gene is selected from the group consisting of *YFL030W* and *YNL194C*.

11. **(Amended)** A method for identifying a target gene product of a bioactive compound, the method comprising the steps of:

contacting a **yeast** host cell with a bioactive compound, wherein the host cell is altered in expression of a target gene product; and

detecting a level of expression of a stress response gene by the host cell in response to said contacting;

wherein a ~~low~~ **lower** or undetectable level of expression of the stress response gene in the host cell relative to a level of expression in a wildtype host cell exposed to the bioactive compound indicates that the host cell is altered in expression for a target gene product that is involved in mediating resistance or sensitivity to the bioactive compound.

13. **(Amended)** The method of claim 11, wherein at least two or more heterozygous deletion strains are contacted with the drug in a single culture, and wherein expression of the reporter gene construct in each ~~strain~~ **host cell** provides for a unique detectable signal for detection of reporter gene expression.

15. **(Amended)** The method of claim ~~14~~**11**, wherein the stress response gene is selected from the group consisting of *HSP26*, *HSP12*, *HSP42*, *HSP78*, and *HSP82*.

16. **(Amended)** The method of claim ~~14~~**11**, wherein the stress response gene is selected from the group consisting of *YFL030W* and *YNL194C*.

17. **(Amended)** A method for determining the drug resistance or sensitivity of a **microorganism** ~~microorganims~~, the method comprising the steps of:

contacting a microorganism with a drug**, wherein said microorganism is a yeast comprised in a biological sample obtained from a subject suspected of having an infection with the microorganism**; and

detecting expression of a stress response gene by the microorganism in response to said contacting;

wherein expression of the stress response gene by the **microorganism** ~~**micoorganism**~~ in the presence of the drug indicates that the microorganism is sensitive to the drug.

20. **(Amended)** A kit for use in determining the drug resistance or sensitivity of a microorganism, the kit comprising:

a control **yeast** host cell; and

a reagent for detection of expression of a stress response gene in the control host cell and in a test sample suspected of comprising a microorganism for which drug resistance or sensitivity is to be determined.